UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/643,233	08/18/2003	Peter Lobel	601-1-077DIV1	3315

23565 7590 10/18/2006

KLAUBER & JACKSON
411 HACKENSACK AVENUE
HACKENSACK, NJ 07601

EXAMINER	
SINGH, ANOOP KUMAR	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/643,233	LOBEL ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17 and 18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/7/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response and amendment to claims filed August 7, 2006 has been received and entered. Applicants have amended claims 17 and 18, while claims 1-16 and 19-30 have been canceled claims

Claims 17-18 are pending.

New Grounds of Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working example are not disclosed in the specification, therefore enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore, skepticism raised in enablement rejections are those raised in the art by artisan of expertise.

Claim 17 is drawn to a method for treating late infantile neuronal ceroid lipofuscinosis (LINCL) by increasing the levels of CLN2 in cells of an animal. Claim 18 limits the increasing level of CLN2 to include administration of CLN2 to the animal. Subsequent claim limits the increasing the level of CLN2 of claim 18 to include a recombinant vector to the affected cell wherein expression vector provides expression of the CLN2 *in vivo*.

The aspects considered broad are: the breadth of subject population, any method of increasing the level of CLN2 by administering AAV vector comprising the nucleic acid encoding CLN2 polypeptide and increasing the levels of CLN2 in any cell of CNS to treat LINCL (a neuro-degenerative disease).

It is noted that as recited, claimed invention reads on a broad genera of gene therapy. Specific considerations for *in vivo* gene therapeutic transfer such as fate of the DNA vector itself (e.g. volume of distribution, rate of clearance into tissue) and consequences of altered gene expression and protein production, have to be addressed for an *in vivo* protein or gene therapy method of treating LINCL in an animal. Although Applicant's specification teaches role of CLN2 in progression of LINCL, the specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to (i) how an artisan of skill would have practiced the claimed method in any animal, (ii) the claimed method would have resulted in providing the CLN2 in deficient cells in amount sufficient to treat any LINCL disorder caused by the deficiency of CLN2 by administering CLN2 or nucleic acid encoding CLN2 protein to any site. An artisan

would have to carry out extensive experimentation to practice the invention, and such experimentation would have been undue because art of gene/ protein therapy and gene delivery *in vivo* is unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced in animals. As will be shown below, these broad aspects as well as limitations were not enabled for the claimed invention at the time of filing of this application because neither the specification nor the art of record taught sufficient guidance to practice the claimed invention. For purposes to be shown in the state of the prior art, the question of lack of enablement is discussed.

The specification teaches that the invention relates to LINCL-associated gene CLN2 and gene product and methods for diagnosing and treating LINCL (pp 2-4). Pages 5-9 broadly summarize the invention and provide a brief description of figures. Pages 10-43 provide a detailed description of preferred embodiments, definition of terms, antibodies of CLN2, detection of CLN2 and therapeutic aspects of CLN2. Pages 44-46 describe therapeutic aspect of LINCL by delivering CLN2 for the treatment.

However, such broad disclosure does not demonstrate the information required by the Artisan to reasonably predict that any protein or transgene can be expressed in at any cell of any animal at therapeutic effective levels. The art of protein and gene therapy and their delivery at the time of the filing of this application was unpredictable wherein any gene was expressed in an individual suffering from CNS disorder.

While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to be desired organs continued to be unpredictable and inefficient. For example, numerous factors complicate the gene delivery art that cannot be overcome by routine experimentation. These include, the fate of DNA vector itself, volume of distribution, rate of clearance in tissue, the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of RNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ significantly based on the vector used and the

protein being produced (Goodman & Gilman's The Pharmacological basis of Therapeutics, McGraw-Hill, New York, NY. pp 77-101).

Given this lack of reasonable predictability in Applicant's specification and the art, the Artisan would require a large amount of information from Applicant's examples to provide the guidance to provide reasonable predictability.

Applicant's examples describe isolation, identification and characterization of CLN2 and corresponding gene product (pp 47-49). It is noted that specification teaches the role of CLN2 in LINCL (example 2) in patients, however specification fails to describe any therapeutic benefit by delivering nucleic acid encoding CLN2 protein to any cells.

At the time of filing, gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses or plasmid DNA/liposome complexes, was considered highly unpredictable. Verma et al states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene " (Verma et al, 1997, Nature, 389, pp 239, col. 3, para 2). Marshall (Science, 1995; 269, 1050,1052-55) concurs, stating that" difficulties in getting genes transferred efficiently to target cells and getting them expressed-remains a nagging problem for the entire field", and that many problem must be solved before gene therapy will be useful for more than the rare application" (Marshall, 1995, 269, pp 1054, col. 3, para 2 and pp 1055, col. 1).

The specification does not disclose the effectiveness of the method of the instant invention in treating LINCL. Nor does it teach the effectiveness of the method in increasing the level of CLN2 in any cell and reversal of any pathology associated with LINCL. The specification only teaches role of CLN2 in progression of LINCL, but fails to disclose any method in treating LINCL. In summary, specification as filed does not teach how nucleic acid encoding CLN2 administered via intracranial route to any mammal that could transduce any cells of CNS such that any active CLN2 is translated. Furthermore, It is noted that the specification does not provide any guidance as to how much vector should to be delivered for transduction of cells in organ of any animal that

would be adequate for therapeutic response. The method of gene therapy and gene delivery in a animal specifically in humans was not routine, rather was unpredictable at the time of filing of this application as neither art of record nor the specification teaches how to practice the claimed inventions.

The method disclosed in specification does not provide any specific guidance that sustained expression of any gene could be achieved by administering transgene by intracranial route to any cell of the CNS. Furthermore, the state of the prior art effectively summarized by the reference of Carter et al (British Journal of Psychiatric, 2001, 178: 392-394) while reviewing the state of gene therapy in CNS conclude, "Advances in gene transfer technologies now provide an array of versatile tolls for gene delivery to localized or wide spread area of the brain. However, the optimism generated by the results in animal models must be tempered because many improvements in safety, efficacy, stability and regulation of gene transfer are required before clinically effective gene therapy can be accomplished in human patient." Carter et al further state that gene therapy attempts in organs with greater accessibility than brain have so far met with disappointing outcome, suggesting that at the time of filing of this application gene therapy strategies in treating CNS disorder was limited to preclinical animal models with some potential to make CNS gene therapy an achievable goal in humans (pp393, last paragraph). Furthermore, in spite of greater flexibility with AAV vectors and its usefulness in physiological research, Shevtsova et al (2005) in a post filing art emphasized that selecting a right vector with an appropriate combination of promoters and serotypes remains an important issue to consider for any gene therapy (emphasis added) (pp 58, left column, 2nd paragraph).

Next, it is noted that because the mechanism of development of each disease is different, the parameters of treating any particular LSD (providing the cell with active enzyme), will be different, from those used in treating another disease such as LINCL and therefore, the reversal of the symptoms in one case due to gene therapy can not be predictive of the effects in another. Such parameters will include the site of action of the enzyme, cell types and tissues affected by the enzyme deficiency (Schuchman EH, Chemistry and Physics of lipids 102: 179-188, 1999; pp 187 left column, 2nd paragraph).

Therefore, the strategy for administering any one enzyme for the treatment will be determined by consideration of cell type, mode of action of enzyme and the organs affected and will be critically different from those from another enzyme and an artisan could not rely on the results obtained in animal model of one disease to extrapolate to any other disease model. Barranger et al (Neurochemical Research, 1999, 24, 601-615), while reviewing the state of the art of gene transfer approaches to the lysosomal storage disease, summarized some of the unpredictability issues associated with the treatment method of lysosomal enzyme deficiency diseases. "The approaches and results present in this paper indicate that gene transfer as a therapy for lysosomal storage disorder requires a significant amount of laboratory and clinical investigation. A variety of studies employing several different systems will be necessary to decide which of the approaches will be effective for these disorders, each of which has its own unique characteristics and complications". The specification does not provide any specific guidance how CLN2 could be delivered to an animal such that enough of CLN2 is made for appropriate time for the treatment of LINCL.

The specification also contemplates using cationic liposome of delivering CLN2 to the target cell. However, there are art-recognized limitations of using cationic liposome for DNA delivery *in vivo* and there is no teaching or contemplation as to how an artisan of skill would have addressed these limitations. For example, Filion et al (Br J Pharmacol. 1997;122(3): 551-557) listed several adverse effects associated with cationic lipids or cationic liposome (table 2, pp 18) such as immuno modulation of animals, complement activation, induction of pulmonary inflammation and toxicity. The specification does not provide any guidance as to what doses of the cationic lipid would be used in the method without eliciting adverse effects. It is noted that the prior art at the time of filing of this application did not provide any guidance in this regard either.

Davis et al (Current Opinion in Biotechnology 2002, 13:128–131) evinces an optimistic outlook for non-viral delivery system but states "perfect system does not currently exist". Davis et al describe problems associated with non-viral gene delivery system, which includes obstacles in manufacturing, toxicity, formulation and stability.

It is noted that as amended claims 17 and require administering AAV vector comprising nucleic acid encoding CLN2 via intracranial route to transduce cells of the animal. However, art of axonal or other retro grade transport in different mammal is unpredictable. The specification teaches therapeutic composition comprising delivery of the invention may be introduced by plurality of routes including intracranial administration. However, specification does not provide any specific guidance to an artisan as to how the composition comprising nucleic acid is administered to any animal such that transgene is expressed in cells that are deficient in CLN2 for appropriate period to elicit desired pharmacological effect. Vite et al., (Gene Therapy, 2003 10, 1874–1881) in a post filing art disclose unpredictability in axonal and retrograde transport of transgene expression in the brain of cat and mouse. Vite et al., suggest substantial evidence of axonal transport in the mouse brain is not evident until 12 weeks post-transduction. Since the cat brain is significantly larger than the mouse brain, with correspondingly longer axons, it is possible that evidence of axonal transport would not be found until much later than 10 weeks after viral injection. Although unlikely, it is also suggested that that the differences in axonal transport of lysosomal enzymes could exist between species. Vite et al summarize major problem in treating the brain in inherited metabolic disorders is delivering the gene or its protein product globally (pp 1878, right column, paragraph 1). It is clear that global gene expression in the mouse brain can be achieved but it is more difficult to achieve global expression in a larger brain. The brain of a child is 1000- 2000 times larger than the mouse brain (pp 1874, paragraph 1). Vite et al emphasize studies involving gene transfer to larger regions of the brain in larger animal model should be initiated before starting human gene therapy trials. In the instance case, the specification only contemplates administering plurality of vector and other means to administer CLN2 in an animal. Because of the art, as shown above, does not disclose how the claimed vectors would be effective in human or even larger animal, the Artisan could not predict, in the absence of proof to the contrary, that such methods as Applicant claims would be efficacious in therapeutic treatment as administering AAV vector encoding CLN2 may only have partial localized effect in human. An artisan would have to carry out extensive experimentation to make use the

invention, and such experimentation would have been undue because of the art of gene therapy and gene delivery *in vivo* in human is unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced.

In conclusion, in view of breadth of the claims and absence of a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for the claimed inventions. The specification and prior art do not teach a method of *in vivo* delivery of CLN2 such that it transduces cells sufficiently to elicit a pharmacological response for a desired duration in the brain of subject suffering from LINCL. An artisan of skill would have required undue experimentation to practice the method as claimed because the art of gene therapy and *in vivo* delivery and treatment of any neurodegenerative condition in general by gene delivery *in vivo* was unpredictable at the time of filing of this application as supported by the observations in the art record.

Response to Arguments

Applicant's arguments filed August 7, 2006 have been fully considered but they are not fully persuasive. Applicants in their argument state that a number of passages in the specification teach presently claimed method in sufficient detail for a skilled practioner to practice the instant invention without any undue burden. Applicants also cite a number of references of Samulski et al 1987, J. Virol. 61: 3096 and Samulski et al., 1989, J. Virol. 63:3822-3828; Davidson et al. (2000, Proc. Natl. Acad. Sci. 97:3428-3432) in support of using AAV vector for delivering transgene for the gene therapy methods. Applicants further assert that intracranial administration as recited in the instant application was also known in the art that is supported by a number of post-filing arts.

In response, it is emphasized that as amended claims embrace a method for treating LINCL by increasing the level of CLN2 in cells of the animal by intracranially administering a AAV vector to CNS cells of the animal. As stated in previous office action dated 4/4/2006, numerous factors complicate the gene therapy art that cannot be overcome by routine experimentation. The specification does not provide evidence to

support that method as recited would results in expression of transgene sufficiently to elicit a pharmacological response for a desired duration in the brain of human suffering from LINCL disease. It is noted that both references of Samulski et al merely describes ability to produce pure populations of infectious viral particle and none of these references teach any specific method to treat LINCL disorder. With respect to post filing teaching of Davidson et al, Examiner agrees with the applicants that post filing art does indicate potential of expressing transgene in CNS, however, disclosure by Davidson or others cited in the paper do not demonstrate if nucleic acid encoding CLN2 is translated in enough of quantity in cells that are deficient in CLN2 for the treatment of LINCL disorder. Prior art teaches that numerous factor including fate of vector, volume of distribution, rate of clearance in tissue, the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of RNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced significantly differ depending on protein being produced as described in previous office action. Thus, it is apparent an artisan would have to perform undue experimentation in order to determine if enough of CLN2 protein is made in cells of CNS.

In support of their arguments, Applicants submit several post-filing art for consideration that includes: Skorupa et al., Exp. Neurol. 1999, 160:17-27; Bosch et al., Mol. Ther. 2000, 1:63-70; Sferra et al., Hum. Gene Ther. 2000, 11:507-519; Frisella et al., 2001, supra; Matalon et al., Mol. Ther. 2003, 7:580-587; Passini et al., J. Virol. 2003, 77:7034-7040; Passini et al., Mol Ther. 2005, 11:754-762; Cressant et al., J. Neurosci. 2004, 24:10229-10239; Desmaris et al., Ann. Neurol. 2004,56:68-76; Griffey et al., Neurobiol. Dis. 2004, 16:360-369; Klugmann et al., Mol. Ther. 2005, 11:745-753; Raft et al., Mol. Ther. 2005, 11:734-744; and Vite et al., Ann. Neurol. 2005, 57:355-364) (see page 6). Applicants assert that effectiveness of AAV vectors for the treatment of mouse and cat models of LSD is described in the citations affirming the applicants argument that method disclosed in instant application is fully enabled. Applicants

describe the teaching of post filing art of Sondhi et al., Haskell et al and Passini et al to support their argument. Applicants in particular assert that Passini et al (2006, J of Neuroscience 26: 1334-1342) discloses AAV-mediated gene delivery of CLN2 to the CNS results in a reduction in pathological features of LINCL in mouse model of the disease and therefore support AAV gene therapy to treat human patient afflicted with LINCL (see page 6, paragraph 1 and page 8).

In response, it is emphasized that as amended claims of instant inventions recite a methods intended for treating LINCL in any animal by increasing the level of CLN2 in cells of the animal by administering a recombinant AAV to CNS cells of the animal, wherein AAV vector is administered intracranially and comprises nucleic acid sequence encoding CLN2 polypeptide comprising SEQ ID NO: 3. It is noted that most of the cited references are not directed to a method for treating LINCL rather they teach generic potential of CNS gene therapy using AAV. The intent is not that AAV cannot be transduced in CNS, rather real issue is whether applicants or prior art provide sufficient guidance to an artisan to practice claimed method at the time of filing of this application. As discussed before mechanism of development of each CNS disease is different, the parameters of treating any particular LSD (providing the cell with active enzyme), will be different, from those used in treating another disease such as LINCL and therefore, the reversal of the symptoms in one case due to gene therapy can not be predictive of the effects in another. Such parameters will include the site of action of the enzyme, cell types and tissues affected by the enzyme deficiency (Schuchman EH, Chemistry and Physics of lipids 102: 179-188, 1999; pp 187 left column, 2nd paragraph). Therefore, the strategy for administering any one enzyme for the treatment will be determined by consideration of cell type, mode of action of enzyme and the organs affected and will be critically different from those from another enzyme and an artisan could not rely on the results obtained in animal model of one disease to extrapolate to any other disease model as stated before (supra). The specification provides a description that is not sufficient to provide enabling support because the claimed therapy method cannot be actually reduced to practice until the skilled artisan is provided by sufficient guidance to specific site of intracranial injection, serotype and titer of AAV that would be sufficient to

infect appropriate number of cells to elicit pharmacological response in an appropriate animal model. These methods would have required undue experimentation because neither the specification nor the art of record teaches specific guidance in this regard. It is further emphasized that post filing cited art of Passini et al (2006) or other as summarized in applicants argument cannot be used for the enabling support of the instant claims as cited arts use method that is different from the instant disclosure and does not provide guidance to other issues raised in this office action. In the instant case, Passini et al disclose gene therapy of CNS in a transgenic knockout mouse model that was disclosed after filing of this application and closely mimics the human pathology of LINCL. It is further noted that 3 ul (6.0×10^8 gc) AAV vector is injected into two sites along a single needle tract in the thalamus (2.00 mm caudal to bregma, 1.75 mm right of midline, 3.50 mm ventral to pial surface) and hippocampus (2.00 mm caudal to bregma, 1.75 mm right of midline, 1.75 mm ventral to pial surface) of the right hemisphere for a total of 6 µl (1.2×10^9 gc) per brain. In addition, Passini et al also disclose comparison of different serotype in the instant study. The injections in both the pilot and serotype comparison studies are performed at a rate of 0.5 µl/min, and the needle is left in place for 2 min after each injection to minimize upward flow of viral solution after raising the needle (see page1335 of Passini et al The Journal of Neuroscience, 2006, 26, 1334-1342 of the record). The disclosure in instant application provided no guidance in terms of site; titer, serotype and animal model that would provide date that could be extrapolated to any subject as embraced by the claims. Therefore, any study that uses a specific model that uses specific site of intracranial injection or any other serotype or titer other then one disclosed in instant application cannot be enabling support. Furthermore, it is noted that even several after filing of instant application Passini reference concludes that this study provides proof of principle of human CLN2 cDNA to the diseased brain only as promising strategy for treating LINCL. Thus, it is apparent that delivery and efficient transduction of CNS cells by gene delivery for the treatment of LINCL was not completely resolved at the time of filing of this application. In absence of any such explicit teaching, a skilled artisan would have to determine the various specifics and would have to perform undue experimentation to test claimed method in

an animal model that shows human pathology of LINCL by administering intracranially at specific location using specific serotype of AAV for appropriate time to elicit pharmacological response. These would have required undue experimentation because neither the specification nor the art of record provided any specific guidance in this regard at the time of filing of this application.

Withdrawn-Claim Rejections - 35 USC § 112

Claims 17-18 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of claim amendments, however, upon further consideration a new ground(s) of rejection is necessitated by the amendments that includes nucleic acid encoding amino acid sequence that is 90% homologous to SEQ ID NO:3.

New-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 17 is drawn to a method for treating late infantile neuronal ceroid lipofuscinosis (LINCL) by increasing the levels of CLN2 in cells of the animal by administering intracranially a recombinant AAV vector comprising a nucleic aid sequence encoding a CLN2 polypeptide or a nuclei acid sequence encoding a CLN2

polypeptide comprising an amino acid sequence 90% homologous to SEQ ID NO: 3. Claim 18 limits the method of claim 17 to include recombinant AAV vector comprising a nucleic acid sequence encoding a CLN2 polypeptide comprising SEQ ID NO: 3.

Thus, claims embrace nucleic acid encoding a polypeptide comprising SEQ ID NO: 3 or a nuclei acid sequence encoding a CLN2 polypeptide comprising an amino acid sequence 90% homologous to SEQ ID NO: 3.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1 117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

The specification describes complete structure nucleic acid and amino acid sequence of human CLN2 in one species. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification does not provide any disclosure as to what would have been the required structure in various species of mammals or how does it vary. The specification also fails to disclose additional representative species of CLN2 nucleic acid and amino acid sequence by any identifying structural characteristics or properties. Based upon the prior art there is expected to be sequence variation among the species of CLN2 sequences. The specification has provided the description of human CLN2. In addition, specification also teaches sequences that are substantially homologous can be identified by comparing the sequences by software, or by hybridization under stringent conditions (see specification page 17 of the specification). However, the specification has not disclosed the sequences of any of the other fragments embraced by the claims. There is no evidence on the record of a relationship between the structures of the DNA molecules of any of the fragment that is 90% homologues to the SEQID NO:3 that would provide any reliable information about the structure of DNA molecules within the genus. There is no evidence on the record that any one of such a homologous fragment

had known structural relationships to each other. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification does not provide any disclosure as to what would have been the required structure in various species of mammals or how does it vary. Furthermore,it is emphasized as discussed above hybridization is set forth in claimed sequence, however the specification does not provide any functional properties to the resulting sequence. For example, a sequence of that is homologues to SEQ ID NO:3 will hybridize, however if it does not contain the essential motifs that are required for contemplated biological activity, such a sequence will hybridize to nucleic acid encoding CLN2 polypeptide but will not be functional and show contemplated biological activity. The claimed invention as a whole is not adequately described if the claims require essential or critical elements or motifs which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Pfaff v. Wells Electronics. Inc.*, 48 USPQ2d 1641, 1646 (1998).

In the instant case, the claimed embodiments of nucleic acid sequence endoing CLN2 polypeptide comprising an amino acid sequence 90% homologous to SEQ ID NO:3, other than the nucleic acid encoding protein set forth as SEQ ID NO: 3 encompassed within the genus of lack a written description. The specification fails to describe what molecules fall into this genus. The skilled artisan cannot envision the detailed chemical structure of the encompassed by the 90% homologous sequence, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 UsPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by member of the genus of homologous of SEQ ID NO: 3, other than the full length sequences showing contemplated biological activity. Therefore, Applicant was not in possession of the genus of homologous sequence to SEQ ID NO:3 as encompassed by the claims. *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

Withdrawn-Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-18 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of amendments to the claims.

Conclusion

No Claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272- 0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anoop Singh, Ph.D.
Examiner, AU 1632

Joe Woitach
AU 1632